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Use of microwave irradiation for sugar and nucleoside phosphonates synthesis

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Abstract—Sugar and nucleoside phosphonates have been prepared using a microwave-assisted reaction. The comparison of thermal and microwave experimental conditions of the Michaelis–Arbuzov reaction is reported.
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Sugar and nucleoside phosphonate derivatives are valuable intermediates for the synthesis of potential therapeutic compounds.[1,2] In recent years, the preparation of such derivatives has attracted attention due to their biological activities, especially as nucleotide analogues having antiviral properties.[3] In addition sugar phosphonates are useful intermediates in the synthesis of various organophosphorus compounds.[4]

Although several synthetic methods are described for the preparation of such compounds, one of the most versatile is the Michaelis–Arbuzov reaction. Unfortunately, it presents some drawbacks when using classical conditions such as length of reaction time, high temperature and removal of the trialkyl phosphite used in a large excess. These drastic conditions may be responsible for side reactions, low yields and limits the application of such reactions to sensitive substrates. Thus, we decided to explore the use of microwave (MW) irradiation to enhance the Michaelis–Arbuzov reaction applied to sugar and nucleoside phosphonate synthesis. Indeed, despite the considerable and still growing interest on the application of microwaves in organic synthesis[5,6] only a few reports have been made in the field of organophosphorus chemistry.[7–10] Furthermore, we carried out microwave experiments using a single mode cavity synthesizer, allowing us to ensure reproducibility and safety.

Starting materials, that is, iododerivatives (Table 1, substrates **1**–**4**) were prepared from previously or recently developed in-house procedures and the corresponding di(ethyl)phosphonates were firstly obtained under thermal conditions. All compounds were fully characterized (NMR, MS, microanalysis ...). The optimization of the reaction conditions under microwave irradiation was investigated using a model substrate (Scheme 1, compound **1**) and triethylphosphite. The reaction progress was monitored using TLC and ^{31}P NMR, and various experimental conditions were studied such as temperature (range of 160–220 °C), reaction time, power of the irradiation (range of 150–300 W), quantity of triethylphosphite engaged. This last factor is of particular importance because the removal of the reagent excess usually required fastidious and long high-vacuum evaporation.
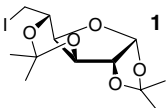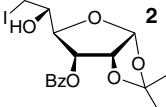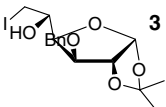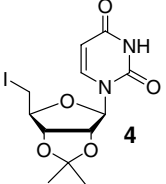
^{31}P NMR experiments enable us to follow the disappearance of the triethylphosphite and the formation of the desired phosphonate **5** as well as the expected side product, (diethyl)ethylphosphonate (Scheme 1). The reaction did not proceed when both the irradiation power was under 300 W and the temperature kept below 180 °C. Selected data of the study are presented in the following graphs and all these experiments were carried out on the same scale using 5 equiv of triethylphosphite over iododerivative **1** and an irradiation power of 300 W. At 180 °C (Graph 1), a small amount of the desired phosphonate **5** was observed and triethylphosphite was still present after 5 h.

Increasing the temperature to 200 °C (Graph 2) allowed the reaction to proceed but required 5 h. The optimized

Table 1. Comparison of thermal and microwave experimental conditions and isolated yields for the studied sugar and nucleoside derivatives

| Substrate	Thermal heating				Microwave irradiation, 300 W[a]			
	P(OEt)$_3$ (equiv)	Temperature (°C)	Time (days)	Isolated yield (%)	P(OEt)$_3$ (equiv)	Temperature (°C)	Time (min)	Isolated yield (%)
1	15	110	3	60	5	220	90	50
2	25	100	2	70	5	180	30	63
3	10	100	2	77	5	200	90	70
4	10	110	3	25	5	200	60	14

[a] All microwave experiments were carried out in a standard 2–5 mL vessel.
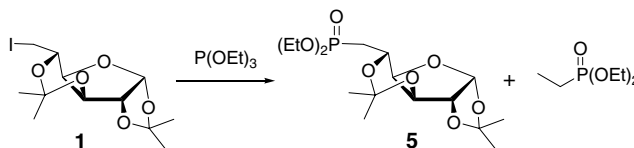
Scheme 1. Reaction carried out for the optimization study.
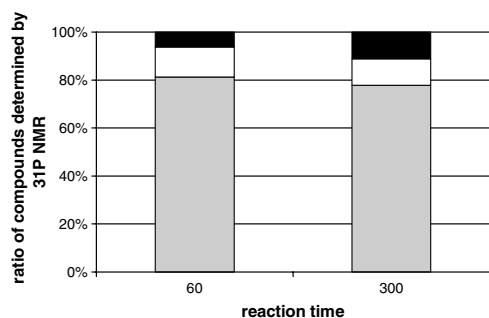
Graph 1. Ratio of triethylphosphite (grey), side product (white) and desired phosphonate (black) observed over time (min) at 180 °C, irradiation power 300 W.
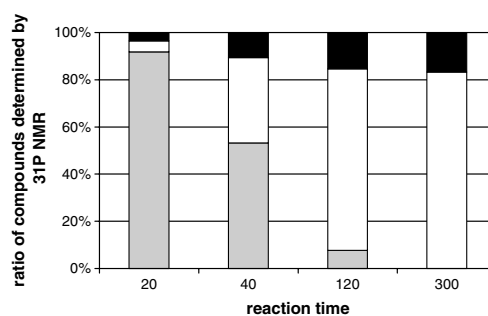
Graph 2. Ratio of triethylphosphite (grey), side product (white) and desired phosphonate (black) observed over time (min) at 200 °C, irradiation power 300 W.

reaction was treating **1** for 90 min at 220 °C, irradiation power of 300 W, with 5 equiv of P(OEt)$_3$ (see Graph 3). This experiment was reproducible (repeated five times) and the reaction scale used was 200 mg to 1.5 g. The attempts to decrease the quantity of P(OEt)$_3$ or stepwise addition did not improve this result in terms of yield of the desired compound **5** and time of reaction. With 1 equiv of P(OEt)$_3$ at 220 °C, at 300 W, and for 15 or 30 min, no reaction was observed either by TLC or

^{31}P NMR. This sequence was repeated three times and yielded 48% of the desired phosphonate after chromatographic separation.

Thus, a similar protocol was applied to other sugars (compounds **2** and **3**) bearing various protecting groups. The comparative results are summarized in Table 1. In all cases, the use of microwaves led to a small decrease of the yield of the corresponding phosphonates after
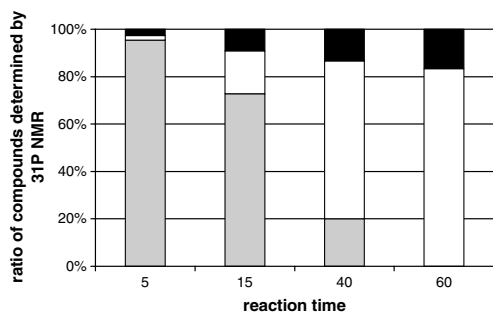
Graph 3. Ratio of triethylphosphite (grey), side product (white) and desired phosphonate (black) observed over time (min) at 220 °C, irradiation power 300 W.

purification. However, the amount of trialkylphosphite engaged was significantly reduced as illustrated for substrate **2**, from 25 to 5 equiv and the reaction time was shortened to 1 h, or less, instead of a few days. Furthermore, we have shown that the MW conditions were compatible with various sugar protections, such as isopropylidene (compound **1**), benzoyl (compound **2**) and benzyl (compound **3**) groups. We then decided to apply the MW conditions to a nucleosidic derivative such as the 5′-deoxy-5′-iodo-2′,3′-O-isopropylidene uridine, **4**. The results were somehow disappointing with this last substrate, in both thermal[11] and MW conditions the corresponding phosphonate[12] was isolated in less than 25% yield. The formation of a dark-coloured reaction mixture and side products were observed in all cases, suggesting a thermal degradation of the substrate.

Microwave irradiation is an effective technique to promote the Michaelis–Arbuzov reaction with short reaction times and reduces the amount of chemical wastes. However, the high temperatures required to perform the reaction under both thermal and MW conditions are still limiting its application to sensitive substrates.

Acknowledgements

References and notes

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12. *Selected physicochemical data for 5′-deoxy-5′-diethylphosphono-2′,3′-O-isopropylidene uridine.* $[\alpha]_D^{20}$ +34.9 (*c* 1.06, MeOH). R_f = 0.5 (CH_2Cl_2/MeOH, 9/1, v/v). ^{1}H NMR (400 MHz, DMSO-d_6, 20 °C): δ = 1.20 (m, 6H, POCH$_2CH_3$), 1.30 (s, 3H, CH$_3$), 2.1–2.4 (m, 2H, H-5′, H-5″), 3.97 (m, 4H, POCH$_2$CH$_3$), 4.25 (m, 1H, H-4′), 4.80 (dd, *J* = 3.6 and 6.4 Hz, 1H, H-3′), 5.10 (dd, *J* = 1.9 and 6.5 Hz, 1H, H-2′), 5.65 (d, 1H, H-5), 5.75 (d, *J* = 1.8 Hz, 1H, H-1′), 7.80 (d, *J* = 8.0 Hz, 1H, H-6), 11.45 (sl, 1H exchangeable, NH) ppm. ^{13}C NMR (100 MHz, DMSO-d_6, 20 °C): δ = 14.7, 14.8 (2d, *J* = 4.3 Hz, POCH$_2CH_3$), 23.7, 25.5 (CH$_3$), 27.9 (C-5′, d, *J* = 137.9 Hz), 59.6, 59.8 (2d, *J* = 4.3 Hz, POCH$_2$CH$_3$), 80.8 (C-4′), 82.1 (C-2′), 82.7 (C-3′, d, *J* = 11.1 Hz), 91.6 (C-1′), 100.4 (C-5), 111.7 (Cq), 142.0 (C-6), 148.0 (C-2), 161.9 (C-4) ppm. ^{31}P NMR (121 MHz, DMSO-d_6, 20 °C): δ = 27.9 ppm. MS (FAB, GT) 405 (M+H)$^+$ and 807 (2M−H)$^-$, 403 (M−H)$^-$, 111 (B)$^-$. UV (EtOH 95°) λ_{max} = 256 nm (ε_{max} = 10200).